Task-specific role of ipsilateral pathways: somatosensory evoked potentials during cooperative hand movements

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Abstract: Task-specific neural coupling during cooperative hand movements has been described in healthy volunteers, manifested by bilateral reflex electromyographic responses in forearm muscles following unilateral ulnar nerve stimulation and by task-specific activation of secondary somatosensory cortical areas (S2) in functional MRI. The aim of this study was to investigate the role of sensory input to the ipsilateral and contralateral cortex during a cooperative task. Somatosensory evoked potentials from the ulnar nerve were recorded over the ipsilateral and contralateral cortex during resting and during cooperative and noncooperative hand movements. Ipsilateral potentials with smaller amplitude were present under all conditions in almost all participants. In relation to the resting condition, the amplitudes of both the ipsilateral and the contralateral potential were reduced during the cooperative and the noncooperative tasks. Nevertheless, the reduction in amplitude was similar for the ipsilateral and the contralateral potentials in the noncooperative task, but less on the ipsilateral compared with the contralateral side during the cooperative task. The ratio of ipsilateral/contralateral somatosensory evoked potential amplitude was thus significantly larger during the cooperative task compared with the control task and the resting condition. This indicates a functional role of ipsilateral pathways connecting the cervical spinal cord with the cortex during the cooperative task. These observations favor the idea of a task-specific mediation of sensory input from both hands to the ipsilateral and contralateral hemispheres as the basis of neuronal coupling.

DOI: https://doi.org/10.1097/WNR.0000000000000285

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Task-specific neural coupling during cooperative hand movements has been described in healthy volunteers, manifested by bilateral reflex electromyographic responses in forearm muscles following unilateral ulnar nerve stimulation and by task-specific activation of secondary somatosensory cortical areas (S2) in functional MRI. The aim of this study was to investigate the role of sensory input to the ipsilateral and contralateral cortex during a cooperative task. Somatosensory evoked potentials from the ulnar nerve were recorded over the ipsilateral and contralateral cortex during resting and during cooperative and noncooperative hand movements. Ipsilateral potentials with smaller amplitude were present under all conditions in almost all participants. In relation to the resting condition, the amplitudes of both the ipsilateral and the contralateral potential were reduced during the cooperative and the noncooperative tasks. Nevertheless, the reduction in amplitude was similar for the ipsilateral and the contralateral potentials in the noncooperative task, but less on the ipsilateral compared with the contralateral side during the cooperative task. The ratio of ipsilateral/contralateral somatosensory evoked potential amplitude was thus significantly larger during the cooperative task compared with the control task and the resting condition. This indicates a functional role of ipsilateral pathways connecting the cervical spinal cord with the cortex during the cooperative task. These observations favor the idea of a task-specific mediation of sensory input from both hands to the ipsilateral and contralateral hemispheres as the basis of neuronal coupling.
***NeuroReport* 25:1429–1432 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

NeuroReport 2014, **25:**1429–1432

Keywords: hand movements, healthy volunteers, ipsilateral potentials, somatosensory evoked potentials, ulnar nerve

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Received 20 July 2014 **accepted** 23 September 2014

Introduction

The neural control of bimanual movements in humans is less well understood than that of unilateral reaching and grasping movements. Cortical structures such as the supplementary motor area [1], the primary and non-primary motor cortex [2,3], the prefrontal cortex [4] as well as subcortical structures such as the corticospinal tract [5] and the reticulospinal tract [6] are assumed to play an essential role. These structures are believed to form distributed neural networks that task specifically control interlimb coordination [7].

Only recently has research suggested that cooperative hand movements, such as opening a bottle, underlie a task-specific neural coupling. This neural coupling manifests itself as a bilateral electromyographic reflex response in the forearm muscles following unilateral ulnar nerve stimulation [8]. The exact mechanism underlying such neural coupling is not yet clear. However, it is likely that ipsilateral fibers of the corticospinal tract, transcallosal connections as well as reticulospinal pathways are involved. In a recent functional MRI (fMRI) [8], specific activation of secondary somatosensory (S2) cortical areas was observed during cooperative hand movements and was assumed to represent a task-specific processing of shared afferent input from both hands during these cooperative movements. The S2 cortical areas are suggested to have similar intracerebral connections as the primary somatosensory cortical areas (S1) [9]. Both the S1 and the S2 areas have ipsilateral connections with each other, as well as with several other cortical areas such as the parietal ventral area (PV), the rostrolateral parietal cortical area (PR), the primary motor cortex (M1), the supplementary motor area, and the limbic cortex [9]. Both S1 and S2 have callosal connections with S2 and PV. In addition, S2 cortical areas are ipsilaterally connected to the ventral part of the frontal cortex, where the ventral stream terminates [9]. The face and trunk areas of S1 cortical areas have additional callosal connections to the contralateral S1 cortical areas, which are projected to both homotopic and non-homotopic areas [10]. In humans, it is suggested that by arm nerve stimulation, S1 and S2 cortical areas become sequentially activated within one hemisphere contralaterally to the side of stimulation with latencies of 20 ms (S1) and 80–100 ms (S2). The ipsilateral S2 cortical area is assumed to be activated in parallel by direct thalamic connections with latencies of 80–100 ms [11]. For ipsilateral fiber tracts, it remains unclear whether the afferent or the efferent signals project ipsilaterally and contralaterally and therefore lead to bilateral responses, or whether a combination of such projections exists.

0959-4965 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/WNR.0000000000000285

Until recently, research has focused on motor pathways mediating bimanual interactions [12]. It has been shown that ipsilateral upper limb muscle responses to transcranial magnetic stimulation can be evoked, although this mainly occurs in axial and proximal limb muscles [13]. The aim of this study was to gain insight into the involvement of ipsilateral somatosensory fibers in neural coupling during cooperative hand movements by analyzing ipsilateral and contralateral somatosensory evoked potentials (SSEPs) following ulnar nerve stimulation. It is hypothesized that ipsilateral afferent pathways are more strongly involved in the control of cooperative hand movements than they are in bimanual control tasks.

Materials and methods

This study was approved by the Ethics Committee of the Canton of Zurich and conformed to the standards set by the Declaration of Helsinki. All participants were informed about the experiment and provided written consent for their participation. The recordings were performed in 13 right-handed healthy volunteers (three men), mean age 26.4 ± 3.7 years and mean height 1.73 ± 0.09 m.

SSEPs were evoked under three experimental conditions: (a) resting (rest), (b) performing noncooperative bimanual in-phase movements in the form of a bilateral pronation–supination task with dumbbells (pro-sup), and (c) dynamic cooperative movements (dyn-coop) performed with a device used previously for the fMRI analysis of cortical activation during cooperative movements [8]. The order of tasks and stimulation side was varied randomly. The volunteers were in a supine position with their eyes closed and lips open and they were asked not to speak or swallow during the recordings to avoid artifacts. The elbows were placed on the bench by the side of the body during all conditions so that only forearm movements occurred. For ulnar nerve stimulation, self-adhesive electrodes (5.96 mm^2; CareFusion, Middleton, Wisconsin, USA) were placed over the ulnar nerve at both wrists with an interelectrode distance of 2 cm. SSEPs were recorded by needle electrodes (12 mm; Spes Medica s.r.l., Battipaglia, Italy) placed over Fz, C3, C4, and Pz. C3 was referenced to Fz to record the contralateral potential during stimulation of the right wrist and ipsilateral potential during stimulation of the left wrist. C4 was referenced to Fz for the measurement of left contralateral and right ipsilateral potential. Pz was referenced to Fz as a control to exclude cephalic signal irradiation that might not be fully subtracted by using the cephalic Fz as a reference. Stimulation intensity was set at 0.5 mA stronger than motor threshold, that is, first visible twitching of the M. abductor digiti minimi. Stimulation frequency was set at 3.1 Hz and two traces at 200 stimulations were applied per side and condition.

SSEPs were elicited and recorded by KeyPoint XP (Medtronic A/S, Skovlunde, Denmark). Signals were transferred to a personal computer for further analysis including filtering, averaging, latency, amplitude, and ratio of amplitude calculation, all of which was performed using Soleasy (ALEA Solutions GmbH Software & Instrumentation, Zurich, Switzerland). A Butterworth band stop filter was used between 45 and 55 Hz to exclude 50 Hz noise from the recorded signal. Latencies were calculated as minima in the time window of 16.5–21.5 ms (N20) and maxima in the window of 20–30 ms (P25). Amplitudes were calculated as the difference between P25 and N20. The ratio of amplitudes between the two sides was calculated as the ipsilateral (stimulation side) amplitude divided by the contralateral amplitude. Time normalization was then calculated by setting the N20 peak of each trace of every participant to 0 and then calculating the average of all traces between 5 ms before the peak and 25 ms after the peak for illustration purposes. Statistics were calculated using IBM SPSS Statistics 19 (IBM Corp., Armonk, New York, USA). Differences in latencies and amplitudes were calculated using Friedman's and Wilcoxon signed-rank tests with Bonferroni corrections.

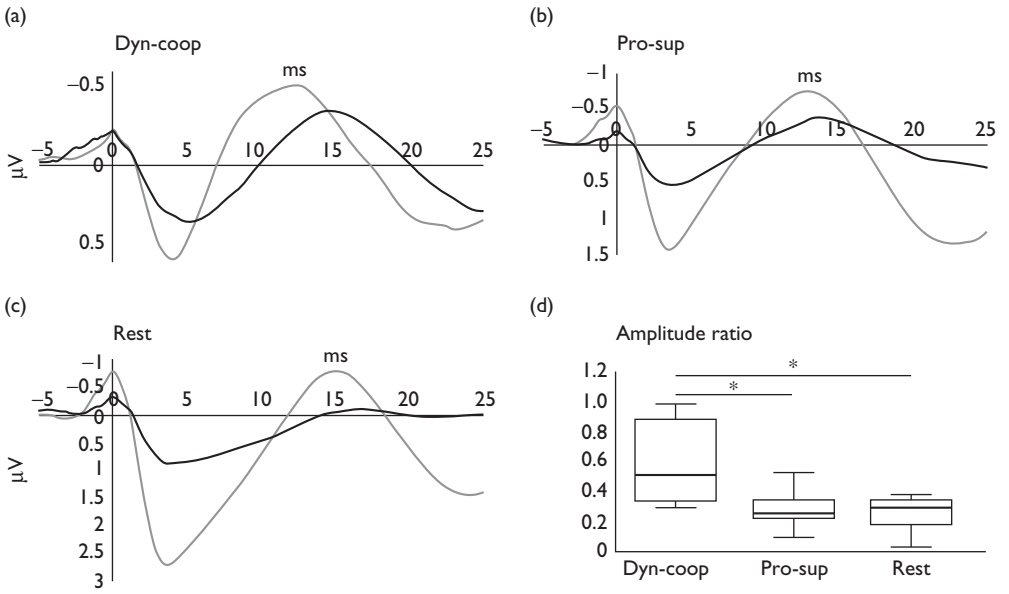
Results

Volunteers could perform the three requested movement tasks while holding the rest of the body and the head still. Only minimal artifacts therefore occurred during the movement tasks compared with the resting condition. The nerve stimulations were perceived, but remained below the pain threshold in all cases. No differences were found in stimulation of the dominant or the nondominant arm, and thus no separation of stimulation site was performed for further analysis. No potentials could be recorded at the Pz location. All participants showed contralateral potentials in all three conditions whereas only 11 of the 13 volunteers showed ipsilateral potentials. These 11 volunteers showed ipsilateral potentials under all conditions, whereas the remaining two participants only showed contralateral potentials.

Figure 1 shows the time-normalized electroencephalography traces for all three conditions (Fig. 1a–c) and the differences in amplitude ratios (Fig. 1d). In the dyn-coop task (Fig. 1a), the N20–P25 amplitude of the ipsilateral side was 0.59 ± 0.33 μV, whereas the contralateral potential had an amplitude of 1.23 ± 0.85 μV. Hence, the ratio for the dyn-coop task was 0.70 ± 0.22. In this task, the ipsilateral N20 latency was 17.84 ± 0.43 ms and the contralateral latency was 18.78 ± 1.56 ms (NS). In the pro-sup task (Fig. 1b), the amplitude ratio was 0.41 ± 0.10, with an ipsilateral amplitude of 0.93 ± 0.31 μV and a contralateral amplitude of 2.34 ± 0.77 μV. The N20 latency was 19.26 ± 1.35 ms on the ipsilateral side and 19.24 ± 1.25 ms on the contralateral side. A similarly low ratio was found in the rest task (Fig. 1c). The ratio was 0.40 ± 0.09 with an ipsilateral amplitude of 1.47 ± 0.42 μV and a contralateral amplitude of 3.85 ± 1.14 μV. The latency was 18.87 ± 1.43 ms for the ipsilateral N20 and 18.98 ± 1.26 ms for the contralateral N20.

The ratio of amplitudes was significantly larger ($P < 0.05$) during the dyn-coop task compared with both the

Fig. 1



(a–c) Time-normalized EEG traces. Average of all participants, N20 at 0 ms. The N20–P25 potentials were evoked during (a) the dyn-coop, (b) the pro-sup tasks, and (c) the resting condition. Gray traces: contralateral potential; black traces: ipsilateral potentials. Note different calibration of ordinate scales. (d) Amplitude ratio: amplitude of ipsilateral potential divided by the amplitude of contralateral potential. Significant differences between dyn-coop and pro-sup as well as dyn-coop and rest. *$P \leq 0.05$. EEG, electroencephalography.

pro-sup and the rest tasks (Fig. 1d). There was no significant difference between the latter two conditions. The absolute amplitudes of ipsilateral and contralateral SSEP were largest during the rest task with significant differences ($P < 0.05$) from the other two conditions for both the ipsilateral and the contralateral potentials. The SSEP amplitudes did not differ significantly between the dyn-coop and the pro-sup task, but there was a trend for larger amplitudes during the pro-sup task compared with the dyn-coop task ($P < 0.08$). The contralateral amplitudes differed significantly from the ipsilateral amplitudes under all conditions. There were no significant differences in SSEP latency between all three conditions.

Discussion

We show, for the first time, that task-specifically modulated, robust ipsilateral SSEPs evoked by electrical stimulation of the ulnar nerve occurred in most volunteers. So far, ipsilateral potentials have only been shown in 10% of patients with epilepsy [14]. These potentials were evoked by electrical stimulation of the median nerve and had a longer latency (up to 18 ms) than the contralateral potentials.

In this study, the ipsilateral potentials were task-specifically modulated and moderately increased in amplitude only in the dyn-coop upper limb task. This finding suggests that the afferent volley induced by nerve stimulation becomes task-specifically gated to the ipsilateral and contralateral cortex, possibly leading to the neural coupling underlying cooperative hand movements [8]. This coupling is reflected in the bilateral reflexes elicited following unilateral nerve stimulation and a bilateral activation of S2 cortical areas in fMRI recordings. The fact that no difference existed in the latencies of the ipsilateral and contralateral SSEPs suggests an involvement of the ipsilateral S1 cortical area as potentials in the S2 cortical area to nerve stimulation have longer latencies (80–100 ms) [11]. It further suggests that the ipsilateral potentials are because of ipsilateral projections from the cervical spinal cord to the cortex and are unlikely because of mediation through transcallosal fibers as such callosal connections would be expected to cause a time difference between the responses in both hemispheres because of callosal delay [15].

The N20 latencies amounted to an average of about 18 ms. This might indicate that this represents the N18 peak generated in the brainstem rather than the N20 peak originating in the cortex. However, the fact that an N18 can only be recorded if a noncephalic reference is used [16] rules this possibility out as our reference was on the cephalic Fz point. Thus, the absence of potentials at the Pz location makes it unlikely that the ipsilateral potentials reflect an irradiation phenomenon instead of a genuine potential.

The general attenuation of ipsilateral and contralateral SSEP during the motor tasks compared with resting might be because of the fact that SSEPs are superimposed on a high background noise because of signals arising during the bilateral movements.

Consequently, the impact of the synchronized volley evoked by electrical stimulation becomes smaller during a movement task in which the afferent pathways are more involved than during rest.

The fact that the ipsilateral potential is less diminished than the contralateral potential during the dyn-coop task, that is, that the SSEP become similar in amplitude, is considered to reflect the task-specific bilateral S2 activation during the dyn-coop task in the fMRI recordings [8]. We suggest that neural coupling during the dyn-coop task is based on the processing of shared input from both hands to the ipsilateral and contralateral S2 cortical areas, respectively, and represented in the bilateral appearance of SSEPs.

The similar latencies of both the ipsilateral and the contralateral potential are in line with the earlier findings of electromyographic reflex responses in both forearms arising with the same latencies [8]. This suggests a task-specific involvement of ipsilateral and contralateral sensory and motor pathways in the control of cooperative upper limb movements. The present study provides evidence toward the mechanisms underlying task-dependent neural coupling. A better understanding of this mechanism will inform rehabilitation of hand function in poststroke patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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